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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,724	12/14/2001	Jeanette McCarthy	MMI-004	5456

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MILLENNIUM PHARMACEUTICALS, INC.
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EXAMINER	
CLOW, LORI A	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 12/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,724	MCCARTHY, JEANETTE	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

Applicant's election without traverse of Group I, claims 1-36, in the reply filed on 28 September 2004 is acknowledged. Claims 37-119 were cancelled.

Priority

Benefit of US Provisional Applications 60/317,178 (filed 5 September 2001) and 60/329,958 (filed 16 October 2001) is acknowledged.

Claim Rejections - 35 USC § 112-Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or

absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must be able to evaluate THBS2, ACE, and FGB alleles to determine a genetic profile of a subject, thereby diagnosing, aiding in the diagnosis, or predicting the likelihood that the subject will develop a vascular disorder. For the reasons discussed below, this constitutes undue experimentation.

b) and c) The specification states the following with respect to the various allelic variations in the present claims:

In one embodiment, the disease or condition is characterized by an aberrant THBS2, ACE, or FGB activity, such as aberrant THBS2, ACE, or FGB protein level, which can result from aberrant expression of a THBS2, ACE, or FGB gene. The disease or condition can be CAD, MI, or another vascular disease. Accordingly, the invention provides methods for predicting a subject's risk for developing a vascular disease associated with aberrant THBS2, ACE, or FGB activity. In a preferred embodiment, a subject having "pattern 1" which comprises two copies of the variant allele of 65755e9 (CC) in combination with two copies of the reference allele of G5755e5 (TT), or the complement thereof, or "pattern 2", which comprises two copies of the reference allele of 65755e9 (TT) and two copies of the variant allele of 65755e5 (GG), or the complement thereof, is at a approximately 3-fold decreased odds of vascular disease compared to all other combinations of genotypes at these two loci.

In another preferred embodiment, a subject having one copy of an A and one copy of a G at nucleotide 86408 of the ACE reference sequence GI 13027555 (AG genotype), or the complement thereof, is at a decreased risk for vascular disease relative to persons with other genotypes for this SNP (c.g., AA or GG genotypes). In yet another preferred embodiment, a subject having two copies of a T at nucleotide residue 5119 of the FGB reference sequence GI 182597, or the complement thereof is at a 3-fold decreased risk for vascular disease relative to persons with the CC genotype. A subject having one copy of a T and one copy of a C at nucleotide residue 5119 of the FGB reference sequence GI 182597, or the complement thereof, is also at a decreased risk for vascular disease relative to persons with the CC genotype.
In still another preferred embodiment, a subject having two copies of an A at nucleotide residue 8059 of the FGB reference sequence GI 182597, or the complement thereof, is at a 3-fold decreased risk for vascular disease relative to persons with the GG genotype. A subject having one copy of an A and one copy of a G at nucleotide residue 5119 of the FGB reference sequence G1 182597, or the complement thereof, is also at a decreased risk for vascular disease relative to persons with the GG genotype (see Example 1). Additionally, the invention provides a method of

identifying a subject who is or is not susceptible to a vascular disorder, which method comprises the steps of i) providing a nucleic acid sample from a subject; and ii) detecting in the nucleic acid sample the presence or absence of a THBS2, ACE, or FGB gene polymorphism, or both in combination, that correlate with the vascular disorder with a P value less than or equal to 0.05 (pages 6-7).

Applicants, however, set forth in the claims the steps of determining the THBS2, ACE, **and** FGB genetic profile to diagnose or predict the likelihood of vascular disease. However, the specification does not teach the combination of all three profiles together as predictive or diagnostic of vascular disease. Furthermore, the specification fails to teach the specific combination of variants for each gene which when taken together would be indicative of the likelihood of developing vascular disease. As shown above, only certain combinations are given, but not combinations in which all three genes with a certain permutation of allelic variation are evidence of vascular disease.

The specification goes on to point to the allelic variation in the individual genes that have been shown to be associated with vascular disease (pages 9-10), but does not address which particular variant alleles from each gene need to be altered such that the "profile" could indicate the likelihood of vascular disease. For example do both polymorphisms in the THBS2 gene need to be present, along with the one in ACE, and the two in FGB? Does one variant cancel another? Are they additive or subtractive? Furthermore, what vascular disease is being diagnosed or predicted? Any vascular disease? The specification fails to teach the methods which are needed to associate variants with any particular vascular disease in any organism. Thus the claims are not enabled.

d) The invention is drawn to methods for diagnosing, aiding in diagnosis or predicting the likelihood of vascular disease with various allelic variants in the THSB2, ACE, and FGB genes.

e) and g) The post filed date art of Lange et al. (Arteriosclerosis, Thrombosis, and Vascular Biology (2002) Vol. 22, pages 418-423) provides evidence that there are major limitations in using coronary artery disease (CAD) endpoints (like myocardial infarction (MI)), as they lead to disease misclassification (see page 418, abstract). Lange et al. go on to teach that CAD is influenced by "the complex interplay of numerous environmental and genetic factors" and that "known risk factors for CAD fail to identify a large proportion of individuals with symptomatic CAD endpoints such as sudden coronary death and MI (page 418, column 1)". Therefore, the art teaches the unpredictability of associating a gene variant or variants with any vascular disease. To practice the broadly claimed invention, one of skill in the art would have to perform large studies in effort to determine the particular combination of variants in THBS2, ACE, and FGB which would lead to a diagnostic method for predicting any kind of vascular disease. Such represents undue experimentation.

f) The skill of those in the art of molecular biology is high.

h) The claims are broadly drawn to "THSB2, ACE, and FGB genetic profile".

The specification teaches identification of polymorphisms at specific residues in SEQ ID NOs: 1, 3, and 5 (GI 307505; GI 13027555; GI 182597, respectively). These "allelic variants" are shown in Tables 1, 4, and 6. Specifically they are (1) a change from thymidine (T) to guanine (G) at residue 3949 of SEQ ID NO:1; (2) a change from (T) to cytidine (C) at residue 4476 of SEQ ID NO:1; (3) a change from adenine (A) to (G) at residue 86408 in SEQ ID NO:3; (4) a change from (C) to (T) at residue 5119 in SEQ ID NO: 5; and (5) a change from (G) to (A) at residue 8059 in SEQ ID NO:5 (page 4). These SNPs have been shown to be identified with vascular disease (page 9). Applicant has defined these five polymorphic variant for SEQ ID NOs: 1, 3,

and 5. There is no description of other mutational site that exist and there is no description of how the structure of SEQ ID NOs: 1, 3, and 5 relate to other alleles that may exist in nature.

The skilled practitioner would first turn to the instant specification for guidance to practice methods. However, the instant specification does not provide specific guidance to practice these embodiments. As such, the skilled practitioner would turn to the prior art for such guidance, however, the prior art shows that such determinations are highly unpredictable, and require substantial additional work and research. Finally, said practitioner would turn to trial and error experimentation. Such represents undue experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 9-11, and 15-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-4, 9-11, and 15-26 recite "the complement thereof". The claims do not adequately define the phrase. The term could have various meanings, such as 100% similarity and the same length as the claimed sequence or it could mean 90% similarity and only a fragment of the claimed sequence. Clarification is requested.

Claims 15-36 recite a method of diagnosing, aiding in the diagnosis, or predicting the likelihood that a subject will or will not develop vascular disease. However, the claims do not

include positive, active method steps such that anything is actually diagnosed or predicted.

Clarification is requested.

No claims are allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center Number is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

MARJORIE MORAN
PATENT EXAMINER
12/7/04

December 7, 2004
Lori A. Clow, Ph.D.
Art Unit 1631